ACETAMINOPHEN, ASPIRIN AND CODEINE PHOSPHATE - acetaminophen, aspirin and codeine phosphate capsule

DESCRIPTION

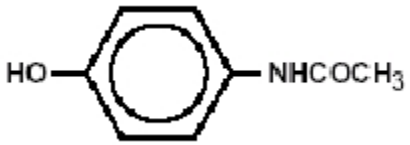
Acetaminophen, aspirin, and codeine phosphate capsules are available in three different strengths and colors:

	150 mg/180 mg/15 mg (grey/green)	150 mg/180 mg/30 mg (grey/black)	150 mg/180 mg/60 mg (grey/red)
Acetaminophen	150 mg	150 mg	150 mg
Aspirin	180 mg	180 mg	180 mg
Codeine* Phosphate	15 mg	30 mg	60 mg

(*WARNING: May be habit forming)

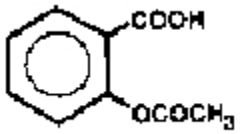
Also contains pregelatinized starch and sodium lauryl sulfate with capsule shells composed of gelatin (containing silicon dioxide and sodium lauryl sulfate as manufacturing aides to the gelatin) with black iron oxide and titanium dioxide as color additives. In addition, the capsule containing 15 mg of codeine phosphate also contains: D&C Yellow #10, FD&C Blue #1 and FD&C Red #40. The capsule containing 60 mg codeine phosphate also contains: FD&C Blue #1 and FD&C Red #40.

Acetaminophen, 4#-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its structure is as follows:



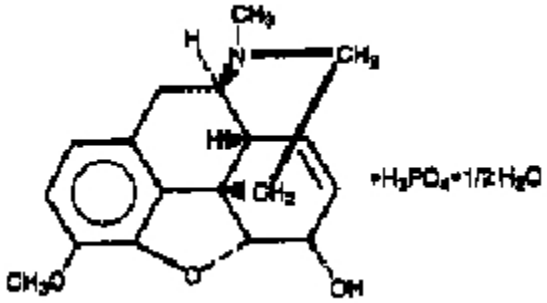
$C_8H_9NO_2$ M.W. 151.16

Aspirin, salicylic acid acetate, is a non-opiate analgesic, anti-inflammatory and antipyretic agent. It occurs as a white, crystalline tabular or needle-like powder and is odorless or has a faint odor, Its structure is as follows:



$C_9H_8O_4$ MW. 180.16

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. Its structure is as follows:



$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2\ H_2O$ M.W. 406.37

CLINICAL PHARMACOLOGY

Acetaminophen, aspirin, and codeine phosphate capsules combine the analgesic effects of a centrally acting analgesic, codeine, with the peripherally acting analgesics, acetaminophen and aspirin. All ingredients are well absorbed orally. The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen, and from 2.5 to 3 hours for codeine. Although aspirin has a half-life of only about 15 minutes, the apparent biologic half-life of salicylic acid in the therapeutic plasma concentration range is between 6 and 12 hours. Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10 percent of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Acetaminophen is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.
Aspirin is rapidly absorbed and almost totally hydrolyzed to salicylic acid following oral administration. Salicylic acid is eliminated by renal excretion and by biotransformation to inactive metabolites. Clearance of salicylic acid in the high-dose range is sensitive to urinary pH and is reduced by renal dysfunction.

INDICATIONS AND USAGE
Acetaminophen, aspirin, and codeine phosphate capsules are indicated for the relief of mild to moderately severe pain.

CONTRAINDICATIONS
Acetaminophen, aspirin, and codeine phosphate preparations should not be administered to patients who have previously exhibited hypersensitivity to any component. Aspirin containing products are contraindicated in patients with bleeding disorders.

PRECAUTIONS

General
Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.
Acute Abdominal Conditions: The administration of this product or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
Special Risk Patients: This drug should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture. Salicylates should be used with caution in patients with gastritis, peptic ulceration or coagulation abnormalities.

Information for Patients
Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.
Caution patients with a predisposition for gastrointestinal bleeding that concomitant use of aspirin and alcohol may have an additive effect in this regard.

Drug Interactions
Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.
The concurrent use of anticholinergics with codeine may produce paralytic ileus.
Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.
Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Pregnancy

Teratogenic Effects

Pregnancy Category C
Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no studies in humans, and the significance of these findings to humans, if any, is not known.

Studies in rodents have shown salicylates to be teratogenic when given in early gestation, and embryocidal when given in later gestation in doses considerably greater than usual therapeutic doses in humans. Studies in women who took aspirin during pregnancy have not demonstrated an increased incidence of congenital abnormalities in the offspring.

This combination product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery
Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, it any, on the later growth, development, and functional maturation of the child is unknown.
Ingestion of aspirin near term or prior to delivery may prolong delivery or lead to bleeding in mother, fetus or neonate.

Nursing Mothers
Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic dosage. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.
Aspirin is excreted in human milk in moderate amounts and can produce a bleeding tendency in nursing infants. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS
The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain and pruritus.
At higher doses codeine has most of the disadvantages of morphine including respiratory depression.
The most common adverse reactions associated with the use of aspirin have been gastrointestinal, including nausea, vomiting, gastritis, occult bleeding, constipation and diarrhea. Gastric erosion, angioedema, asthma, rash, pruritus and urticaria have been reported less commonly. Tinnitus is a sign of high serum salicylate levels (see OVERDOSAGE).
Aspirin Intolerance: Allergic type reactions in aspirin-sensitive individuals may involve the respiratory tract or the skin. Symptoms of the former range from rhinorrhea and shortness of breath to severe asthma, and the latter may consist of urticaria, edema, rash or angioedema (giant hives). These may occur independently or in combination.

DRUG ABUSE AND DEPENDENCE
Acetaminophen, aspirin, and codeine phosphate capsules are a Schedule III controlled substance.
Codeine can produce drug dependence of the morphine type, and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

OVERDOSAGE

Acetaminophen
Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.
In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.
Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.
Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.
The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

Aspirin

Signs and Symptoms: Headache, tinnitus, hearing difficulty, dim vision, dizziness, lassitude, hyperpnea, rapid breathing, thirst, nausea, vomiting, sweating and occasionally diarrhea are characteristic of mild to moderate salicylate poisoning. Salicylate poisoning should be considered in children with symptoms of vomiting, hyperpnea, and hyperthermia.

Hyperpnea is an early sign of salicylate poisoning, but dyspnea supervenes at plasma levels above 50 mg/dL. These respiratory changes eventually lead to serious acid-base disturbances. Metabolic acidosis is a constant finding in infants but occurs in older children only with severe poisoning; adults usually exhibit respiratory alkalosis initially and acidosis terminally.

Other symptoms of severe salicylate poisoning include hyperthermia, dehydration, delirium, and mental disturbances. Skin eruptions, GI hemorrhage, or pulmonary edema are less common. Early CNS stimulation is replaced by increasing depression, stupor, and coma. Death is usually due to respiratory failure or cardiovascular collapse.

Treatment: Since there are no specific antidotes for salicylate poisoning, the aim of treatment is to enhance elimination of salicylate and prevent or reduce further absorption; to correct any fluid electrolyte or metabolic imbalance; and to provide general and cardiorespiratory support. If acidosis is present, intravenous sodium bicarbonate must be given, along with adequate hydration, until salicylate levels decrease to within the therapeutic range. To enhance elimination, forced diuresis and alkalinization of the urine may be beneficial. The need for hemoperfusion or hemodialysis is rare and should be used only when other measures have tailed.

Codeine

Signs andSymptoms: Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) should be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. It should be kept in mind, however, that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects. Equivalently high doses in children would have similar effects.

The dose of this combination product is limited by the amount of codeine phosphate per capsule. For adults, a single dose of codeine phosphate should not exceed 60 mg. For children, the usual recommended single dose is 0.5 mg/kg.

For the capsule containing 15 mg or 30 mg of codeine phosphate, the usual adult dosage is one or two capsules every four hours as needed.

For the capsule containing 60 mg of codeine phosphate, the usual adult dosage is one capsule every four hours as needed.

HOW SUPPLIED

Acetaminophen, Aspirin, and Codeine Phosphate Capsules, 150 mg/180 mg/15 mg, each capsule of which contains acetaminophen 150 mg, aspirin 180 mg, and codeine phosphate 15 mg (WARNING: May be habit forming), are available as an opaque grey body and opaque green capped capsule, imprinted “LPI/LPI” in black, and are supplied in bottles of 100 capsules, NDC 46672-231-10.

Acetaminophen, Aspirin, and Codeine Phosphate Capsules, 150 mg/180 mg/30 mg, each capsule of which contains acetaminophen 150 mg, aspirin 180 mg, and codeine phosphate 30 mg (WARNING: May be habit forming), are available as an opaque grey body and opaque black capped capsule, imprinted “LPI/LPI” in white, and are supplied in bottles of 100 capsules, NDC 46672-230-10.

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Storage: Protect from moisture. Store at controlled room temperature 15-30°C (59-86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:

MIKART, INC.

Atlanta, GA 30318

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